THE RELATIONSHIP OF THE PATHOLOGICAL HISTOLOGY AND THE IODIN COMPOUNDS OF THE HUMAN THYROID.*

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The present study presents some new evidence in the solution of the problems of the relationships between the clinical, pathological, and chemical findings in cases of human goitre. The scope of the study is limited to 566 cases, from which specimens have been analyzed chemically in the course of a general investigation of the iodin compounds of the thyroid. The cases were not selected, but were taken at random in the order as operated on from the patients under treatment in the Mayo Clinic during 1914.

Clinical Classification. The clinical classification of the cases into (1) hyperplastic toxic ("exophthalmic" goitre); (2) non-hyperplastic toxic with high blood-pressure; (3) non-hyperplastic toxic with low blood-pressure; (4) non-hyperplastic questionably toxic with low blood-pressure, and (5) non-hyperplastic atoxic with low blood-pressure has been made by Plummer,[1,2] and follows his previous grouping. Though the terms "hyperplastic" and "non-hyperplastic" refer to the morphology of the gland, which cannot be shown until its removal, yet they have been used in making the clinical diagnoses by Plummer and his associates with but a negligible margin of error, as shown by the subsequent pathological examination.

Pathological Classification. The pathological classification is, with slight modification, that previously published by Wilson.[3-10] The main divisions, (1) primary hypertrophy and hyperplasia of epithelium; (2) primary retention of colloid with atrophy of epithelium; (3) encapsulated adenomas, and (4) carcinomas, with their several subdivisions, are self-explanatory. As our study of the morphology of the thyroid in goitre has progressed, it has been found desirable to subdivide the group of regressing hyperplasias into subgroups, early, advanced, and very advanced regression. Also the undegenerated encapsulated adenomas, with colloid-filled acini, Group G, are so few in proportion to the degenerated adenomas, Group F, that in the present study the three subgroups have not been separated. The encapsulated adenomas have been separated from adenomatoses, and the latter

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disease. In 3 of the cases of chronic glomerulonephritis the eye-grounds were studied, and except for slight edema in one no abnormal findings were noted. The Wassermann serum reaction was negative in the 3 cases in which it was done. The ages of these 4 cases ranged from thirty-eight to sixteen years, which is lower than those of the other group. There were, however, many cases of the vascular type within these age limits.

From a study of this small group of cases of chronic glomerulonephritis it is evident that it will not be possible by means of the four tests for renal disease mentioned above to tell definitely into which group a given case of nephritis belongs. The age of the patient, the presence or absence of edema or pulse pressure also does not give any assistance in this direction. Changes in the eye-grounds were not constant enough in either group to aid in classifying the cases. The previous history is not of assistance, for although most of the cases of glomorulonephritis had scarlet fever, still many of the cases of chronic vascular nephritis that died young also had had scarlet fever. It must be remembered that these cases are all ones of pronounced nephritis in the end stages. It is possible that by the more complicated dietary tests for renal function which may be carried out on the patients not so ill a grouping of the cases according to the pathological lesions may be accomplished. Possibly, therefore, at some future date enough of the chronic nephritis cases that have been studied in this hospital by these more elaborate methods will come to autopsy here to settle this question.

Grouping all these cases for clinical purposes simply as chronic nephritis of a severe grade, it is interesting to note that the non-protein nitrogen of the blood was elevated in all cases but one in which it was examined, and that one may well have died of cardiac and cerebral complications. The ability of the kidney to excrete phenolsulphonephthalein was diminished in all the cases in which it was done. Albumin was present in the first or second urine examinations in all cases but 2. Casts were not found in 3 cases and only rarely in 3 more. The blood-pressure was above 150 in all but 4 of the cases; 7 of the 14 cases in which the fundi were examined showed lesions in the eye-grounds.

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included in the group described as primary retention of colloid with atrophy of epithelium.

CHEMICAL INVESTIGATION. The methods employed in the determination of iodin and the dry weight of thyroid substance removed at operation were as follows:

The fresh gland was placed in a crystallizing dish, covered with a glass plate, and heated three or four hours in an oven at 100° C. This preliminary treatment removed a large portion of the water and made the gland cut more easily into smaller pieces. After the gland was cut into small pieces it was completely dried in a vacuum desiccator, and then ground to a fine powder in a coffee mill, thoroughly mixed, and the iodin content determined[11] in a one-half gram portion. Two modifications of this procedure were employed for some of the glands. Instead of taking the entire fresh gland for purposes of desiccation, a known portion of the total was taken, and from the dried weight of this portion the dried weight of the total gland and the amount of iodin were calculated. The other modification consisted in taking a portion of the gland after it had been fixed in 4 per cent. formaldehyde. From this known portion the dried weight of the total gland was determined, and the total iodin based on this weight. Analysis of the formaldehyde solution showed that in every case an appreciable amount of iodin from the gland had passed into the formaldehyde solution. It was therefore necessary to determine the amount of iodin in this solution to obtain the total iodin originally present in the portion of the gland removed at operation. The results obtained by these procedures were kept separate until after they were compared with the pathological grouping. This comparison showed no appreciable differences between the three methods, so that in the final tabulation of results there was no discrimination made as to which method was employed for determining the total dried weight and the total iodin.

In addition to the determination of the total iodin, the dried thyroid substance of fifty-eight thyroids was hydrolized by a method already published.[13] This hydrolysis splits the proteins into simpler products and divides the total iodin into two chemically different groups. The α-iodin compound is insoluble in acids. The β-iodin compound is soluble. Both α- and β-iodin are in organic combinations, and there is evidence that β-iodin is not a decomposition product of the α-iodin compound, but that the two forms exist independently in the gland. Physiological tests[14] have shown that the α-iodin compound produces the typical effects of desiccated thyroid, but that the β-iodin compound has no toxic action. It therefore seemed desirable to determine the amount of α-, or toxic, iodin compound in some of the glands removed. For the determination of the amount of α-iodin in a given gland, the dry

powdered gland was boiled in 90 per cent. alcohol in the presence of 1 per cent. sodium hydroxide for forty-eight hours, 2.5 grams of the dried thyroid per 100 c.c. of alcohol. At the end of the boiling, carbon dioxide was passed through the solution and the alcohol evaporated. The solution was then acidified with 20 per cent. sulphuric acid. The precipitate (α-constituents) was filtered and washed with a small amount of water. This precipitate was dissolved in sodium hydroxide. The amounts of iodin in the filtrate (β-constituents) and in the solution of the α-constituents were determined. This gave the amounts of α- and β-iodin, and the sum of these two the total iodin in the gland.

In connection with the determination of iodin, it may be said that the results obtained during the course of this investigation approximate 4000 determinations of iodin. From a comparison of duplicates and an inspection of the accuracy of the total series, it would appear that for this work the method used is entirely adequate. The great advantage of obtaining a perfect "blank" where no iodin exists, of having no blue color flashed back from the starch iodin reaction after titration is finished, and the wide range in the amounts of iodin which come within the method, together with the shortness of time and inexpensive chemicals, have made this method the one of choice in our laboratory.

PROTOCOLS. The bulk of the material makes publication of protocols obviously cumbersome. However, the protocols of the chemical analyses and pathological examinations, with the microscopic sections, gross specimens and the clinical histories are on file in the Mayo Clinic, and are open to study to anyone interested. The results have been accurately compiled and condensed into a series of tables herewith presented.

DISCUSSION OF TABLES. *Table I.* The distribution of the cases into the several clinical and pathological groups is given in totals, rather than in averages, that the numbers may serve as a basis for determining the percentage values in subsequent comparisons. It will be observed that the number of cases in certain groups (*A*, hyperplastic toxic; *D*, non-hyperplastic toxic and non-hyperplastic questionably toxic; *H*+*F*, non-hyperplastic toxic and non-hyperplastic questionably toxic; *F*, questionably toxic; and the carcinomas) are so small as to make the averages of relatively little value. However, it would have been more inaccurate to omit these cases entirely, and attention will be called to the insufficient evidence presented in these groups as the several comparative tables are discussed later. It should be noted that of the 425 cases of non-hyperplastic goitre, 197 presented symptoms which might have caused many of them to be diagnosed as "exophthalmic goitres" by clinicians elsewhere. Without analyzing in detail the distribution of these cases, it may be pointed out that the general distribution

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Pathological Classification.	Clinical Classification.	Table I.—Number of Cases.						Table II.—Average Ages (in Years).					
		1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).	1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
1. Primary Hypertrophy and Hyperplasia of Epithelium:													
A. Early hypertrophy and hyperplasia	2	..	..	..	..	2	19	..	..	..	..	..	19
B. Advanced hyperplasia	44	..	..	..	..	44	34	..	..	..	..	..	34
C 1. Early regression of hyperplasia	38	..	..	..	..	38	33	..	..	..	..	..	33
C 2. Advanced regression of hyperplasia	36	..	..	..	..	36	35	..	..	..	..	..	35
C 3. Very advanced regression of hyperplasia	17	..	..	..	..	17	31	..	..	..	..	..	31
2. Primary Retention of Colloid; Atrophy of Epithelium:													
D. Secondary regeneration of epithelium	4	16	5	4	25	54	29	45	40	33	32	32	
H. Diffuse atrophy of epithelium	..	65	35	11	96	207	..	50	37	35	35	40	
H + F. Diffuse atrophy of epithelium with included adenomas	..	27	9	2	47	85	..	49	33	38	36	40	
3. Encapsulated Adenomas:													
E, F, G	..	25	12	7	35	79	..	46	40	44	36	40	
4. Carcinomas	..	3	—	—	1	4	..	44	—	—	42	44	
Totals (average)		141	136	61	21	294	593	35	49	38	38	35	39

closely approximates that shown in a similar group of patients operated on in 1911 and 1912.[9]

Table II. Table II shows the average age of the patients at the time their thyroids were removed. While the average ages of the patients with hyperplastic toxic goitre is thirty-five years, it will be noted that the average age of those with early hypertrophy is only nineteen years, of those with advanced hyperplasia thirty-four years, and of those whose thyroids showed regression in the hyperplastic process it is thirty-eight, thirty-five and thirty-four years respectively, in inverse order to the amount of regression. At first thought, it would appear that this inversion of the average ages in relation to the amount of regression of hyperplasia is contradictory, but when the average ages are examined in the light of Table III, in which is shown the average duration of goitre in months, it will be seen that while the younger patients showed the greatest amount of epithelial regression the duration of the goitre as well as the duration of symptoms were both also inversely as to age and directly as to the amount of regression. The same holds good in the four cases of clinically hyperplastic toxic goitre with secondary regeneration of the thyroid epithelium. Here the average age was twenty-nine years, and though the average duration of goitre was one hundred and thirty-two months, the average duration of symptoms was only eleven months. In this pathological group (epithelial regenerations) the age-distribution of the patients in the various clinical classes is interesting, being twenty-nine years in the hyperplastic toxic, forty-five years in the non-hyperplastic toxic with high blood-pressure, fifty years in the non-hyperplastic toxics with low blood-pressure, thirty-three years in the non-hyperplastic questionably toxic, and thirty-two years in the non-hyperplastic atoxic cases.

The somewhat erratic age distribution of the cases in which the glands showed encapsulated adenomas, either alone (*E, F, G*) or included in diffuse colloid goitres (*H+F*), may not be wholly accidental, but may be due to the influence of the neoplasms. This point, however, is still under investigation in a larger series of cases.

Table III. The average duration of goitres in months for the entire series and the duration of hyperthyroidism in months for the hyperplastic series is shown in Table III. The duration of the symptoms in the toxic non-hyperplastic cases is so difficult to determine with any degree of accuracy from the patient's description that no attempt has been made to state it in months. The difference between the period of duration of goitre in hyperplastic toxics, averaging forty-one months, and the period of duration of goitre in the non-hyperplastic groups (the lowest of which is 156 months, and the highest 276 months, with an average of 192 months) is very marked, and constitutes a point in clinical diagnosis.

TABLE V.—AVERAGE WEIGHT OF REMOVED GLAND (FRESH) IN GRAMS.

TABLE VI.—AVERAGE PER CENT. OF IODIN IN DRIED THYROID.

PATHOLOGICAL CLASSIFICATION.	CLINICAL CLASSIFICATION.	1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).	1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastictoxic (?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:													
A. Early hypertrophy and hyperplasia		46	..	..	..	..	46	0.11	..	..	..	..	0.11
B. Advanced hyperplasia		59	..	..	..	..	59	0.03	..	..	..	..	0.03
C 1. Early regression of hyperplasia		56	..	..	..	..	56	0.07	..	..	..	..	0.07
C 2. Advanced regression of hyperplasia		53	..	..	..	..	53	0.10	..	..	..	..	0.10
C 3. Very advanced regression of hyperplasia		70	..	..	..	..	70	0.19	..	..	..	..	0.19
2. PRIMARY RETENTION OF COLLOID ATROPHY OF EPITHELIUM:													
D. Secondary regeneration of epithelium		42	175	146	151	171	159	0.07	0.08	0.14	0.05	0.05	0.07
H. Diffuse atrophy of epithelium		..	223	169	170	158	181	..	0.08−	0.11−	0.08	0.08−	0.08+
H + F. Diffuse atrophy of epithelium with included adenomas		..	180	112	266	183	170	..	0.09	0.12	0.05	0.06	0.07
3. ENCAPSULATED ADENOMAS:													
E, F, G		..	109	125	140	108	114	..	0.07	0.02	0.01	0.06	0.06
4 CARCINOMAS		....	730	—	—	140	583	..	0.005	—	—	0.07	0.03
Totals (averages)		57	190	150	167	157	137	0.10	0.08	0.10	0.06	0.06+	0.085

the percentage is lowest in the non-hyperplastic atoxic (av. 0.06 per cent.). Attention is called to this inversion of the order of the percentage amounts in relation to clinical symptoms over those observed in the cases of hyperplastic goitre.

A tabulation of both groups of non-hyperplastic toxic cases in comparison with the non-hyperplastic atoxic cases shows that in 84 per cent. of the atoxic the percentage of iodin was under 0.1, while but 68 per cent. of the toxic cases were under 0.1.

Table VII. In the hyperplastic toxic cases, the total amount of iodin in the portion of the gland removed follows the percentage of iodin since the portion of gland removed in these cases is fairly equal in the several groups. The amount averages 9.2 mg. in early hypertrophy, drops to 3.4 mgs. in the advanced hyperplasias, rises to 8 mgs. in the early regressions, to 14.2 mgs. in the advanced regressions, and to 21.9 mgs. in the very advanced regressions. The total amount in the cases with secondary regeneration of epithelium, which showed symptoms placing them in the hyperplastic toxic clinical group, is the smallest of any of the groups except the advanced hyperplastic toxics and carcinomas.

In the non-hyperplastics, the largest amount is in the toxics with low blood-pressure (23.8 mgs.), while in the atoxics the amount averages 15 mgs. It should be noted that though the amount of iodin in the portions of glands removed in the non-hyperplastic cases is greater than the amount removed in the hyperplastic cases, the comparison of the relative amounts in the total gland is not made on the same basis, since in the non-hyperplastics a very much larger proportion of the gland is removed at operation (frequently as much as $\frac{9}{10}$) than is removed at operation in hyperplastic cases (rarely more than $\frac{2}{3}$).

Thus, it is probable that the total amount of iodin in the entire gland in the cases of hyperplastic goitre with very advanced regression averages more than the total amount of iodin in the entire gland in the non-hyperplastic cases.

The averages of the total iodin of patients grouped as to age by half-decades shows no order or regularity, but a similar grouping of the average total amounts of iodin arranged by duration of goitre in half-decades results as follows:

ADDENDUM TO TABLE VII.—TOTAL IODIN AND DURATION OF GOITRE.

Duration of goitre in half-decades.	Non-hyperplastic toxic. Number of cases.	Non-hyperplastic toxic. Average total iodin, mgs.	Non-hyperplastic atoxic. Number of cases.	Non-hyperplastic atoxic. Average total iodin, mgs.
5−	30	19.6	23	13.7
5+	21	18.4	37	12.3
10+	26	21.3	28	16.9
15+	23	32.9	30	16.9
20+	22	28.3	20	22.5
25+	19	22.3	11	14.0
30+	12	22.1	1	13.5
35+	8	28.3	2	16.2
40+	11	28.3	3	16.0

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TABLE VII.—TOTAL IODIN IN PORTION OF GLAND REMOVED (IN MILLIGRAMS).

PATHOLOGICAL CLASSIFICATION.	CLINICAL CLASSIFICATION: 1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia	9.2	..	..	..	..	9.2
B. Advanced hyperplasia	3.4	..	..	..	..	3.4
C 1. Early regression of hyperplasia	8.0	..	..	..	..	8.0
C 2. Advanced regression of hyperplasia	14.2	..	..	..	..	14.2
C 3. Very advanced regression of hyperplasia	21.9	..	..	..	..	21.9
2. PRIMARY RETENTION OF COLLOID; ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium	5.7	19.0	25.0	11.9	12.1	14.9
H. Diffuse atrophy of epithelium	..	28.1	32.8	21.1	18.4	23.0
H + F. Diffuse atrophy of epithelium with included adenomas	..	27.5	22.2	11.1	13.0	18.6
3. ENCAPSULATED ADENOMAS:						
E, F, G	..	13.8	11.6	6.4	10.0	10.0
4. CARCINOMAS	..	5.1	—	—	1.6	4.4
Totals (averages)	9.7	23.8	26.5	14.5	15.0	

TABLE VIII.—AVERAGE PERCENTAGE OF α-IODIN (Number of determinations shown in parenthesis).

1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
7 (1)	..	..	..	..	7 (1)
16 (11)	..	..	..	..	16 (11)
31 (8)	..	..	..	..	31 (8)
31 (6)	..	..	..	..	31 (6)
37 (4)	..	..	..	..	37 (4)
—	—	16 (1)	—	34 (1)	25 (2)
30 (2)	..	33 (4)	38 (1)	35 (6)	34 (13)
..	—	25 (1)	—	18 (1)	22 (2)
40 (1)	27 (2)	—	35 (8)		34 (11)
..	..	..			
25 (30)	30 (3)	28 (8)	38 (1)	34 (16)	(58)

While there are considerable fluctuations in the total amount of iodin present at the different half-decades, the most constant relationship is that at each half-decade the total amount in the toxic cases is materially more than is the total amount in the atoxic cases.

Table VIII. The determination of the α-iodin has been made in too few cases to make the average percentages of much comparative value, there being but 30 cases in the hyperplastic group and 28 in the non-hyperplastic group. It may, however, be noted that in those groups in which a sufficient number of cases exist for comparison, that the following order is presented: In the cases of advanced hyperplasia, the percentage of the total iodin in the α form is 16 (11 cases), and rises to 35 (18 cases) in the advanced regressions. In the non-hyperplastic cases, if the two groups with toxic symptoms are placed together (11 cases), the average percentage of the total iodin in the α form is 30, while in the atoxic group (16 cases) the average percentage is 34. Thus it will be seen that there is a parallel relationship in the two groups, though until further data is obtained no great significance can be attached to it.

GENERAL DISCUSSION. 1. The data herein presented furnishes additional proof of the statements previously made by one of us,[3] that the symptom complex, which is generally recognized as "typical Graves's disease," "exophthalmic goitre," etc., and sharply denoted by Plummer as hyperplastic toxic goitre is constantly parallel in all its stages of development and regression with similar stages of development and regression in the parenchyma of the thyroid. This parallelism is shown in the average duration of goitre, the average duration of toxic symptoms, and in the progressive and regressive histological changes.

Now, for the first time in detail the percentages and total amounts of iodin, the pathological groups, and the clinical types have been compared in the same series of cases. As previously suggested by the work of Smith and Broders,[15] a close parallelism obtains throughout the data from the three sources.

From previous investigations there seemed to be little doubt that the clinical picture of exophthalmic goitre is produced, either directly or indirectly, by hyperactivity of the thyroid; but until some definite substance had been isolated from the normal thyroid and from the pathological glands and shown to be toxic in its nature, no final conclusion could be arrived at. The isolation in pure form of a compound containing 60 per cent. of iodin[12 13 14] and the proof that this substance is highly toxic in nature, emphasized the importance of an investigation concerning the amount and nature of the iodin-containing compounds of the thyroid. It has been shown that the iodin in the glands exists in two independent forms of combination, only one of which, the α form, is toxic. We must therefore enlarge our conception of the physiological action of the iodin compounds

to include the action of this one the toxicity of which is vastly greater than that of any other hitherto described.

It is significant to find that this α-iodin compound is present in the actively hyperplastic glands of advanced hyperplastic toxic goitres in only $\frac{1}{3}^{1}_{0}$ to $\frac{1}{15}$ the amount in which it is present in normal thyroids. This must be interpreted not as a reduced production of the toxic substance but as the result of its greatly increased diffusion from the gland into the blood stream. There is no quantitative measure of the secretory activity of the thyroid, but its storage capacity for the toxic substance is obviously proportional to its iodin content. If further observations support the relatively few herein recorded, it would seem to be a fair assumption that the α-iodin compound is responsible for the toxic symptoms in hyperplastic toxic goitre. The constant direct relationship between the clinical symptoms and pathological picture and the reservoir capacity of the thyroid in hyperplastic toxic goitre is strikingly shown in Tables VI, VII, and VIII. The failure on the part of other pathologists to recognize this constant association, we believe, has been due (1) to failure by clinicians to distinguish sharply between hyperplastic toxic goitre ("typical acute exophthalmic," "Graves's disease," etc.) and the several indeterminate groups of non-hyperplastic toxic goitre ("atypical chronic Graves's disease," "cardiovascular goitre," etc.), and (2) failure to recognize the fact long ago suggested,[3] that the chemical constituents found in the thyroid are only the complement of those which must have gone out of the gland to have caused symptoms.

2. The relationships of the pathology and chemistry of non-hyperplastic thyroids to the various clinical groups of toxic and atoxic non-hyperplastic goitre are still far from being cleared up. This is due (1) to the difficulty in accurately grouping these cases clinically, (2) to the difficulty in securing accurate information as to the onset and course of the chronic symptoms, and (3) to the difficulty in intrepreting long past primary pathological changes in the light of present pathological and chemical findings since most of these patients seek surgical aid many years after the beginning of the goitre, and probably also several years after the beginning of symptoms. That the relationship of the histological changes in the thyroids designated as epithelial regenerations is parallel with the iodin content of the glands, and to some extent with the clinical history of the patients from whom the glands were removed, is shown in the several tables.

One fact running through all the tables is that the amount of iodin in the gland parallels the clinical grouping. In the actively hyperplastic glands (group B) it has been shown that the amounts of iodin and α-iodin are very low, but in cases where regression has occurred (group C) the amounts of iodin are high. In contrast to this it was found that the amount of iodin in the non-hyperplastic toxic glands is higher than in the non-hyperplastic atoxic glands.

The clinical picture, in its most severe type, of patients with non-hyperplastic toxic goitre approaches in many respects the picture of patients with hyperplastic toxic goitre. Assuming the same toxic substance to be the cause for all thyroid intoxication, the factors involved to produce varying clinical pictures, are the daily amount of absorption of the toxic substance, the length of time during which this intoxication occurs, and the personal resistance of the patient. At present we have no conclusive evidence explaining the higher iodin content of toxic non-hyperplastic glands than that of the actively toxic hyperplastic glands, but it seems probable that the diffusibility from the gland of the α-iodin compound may be an important factor in determining whether a goitre produces toxic symptoms or not.

Further rearrangements of the clinical groups of non-hyperplastic goitre are in progress by Plummer, and further studies of the pathology and chemistry of the thyroids from these cases are now being made by us and will be reported later.

REFERENCES.

1. Plummer, H. S. The Clinical and Pathological Relationships of Simple and Exophthalmic Goitre, Amer. Jour. Med. Sci., 1913, cxlvi, 790–796.

2. Plummer, H. S. The Clinical and Pathological Relationships of Hyperplastic and Non-hyperplastic Goitre, Jour. Amer. Med. Assn., 1913, lxi, 650–651.

3. Wilson, Louis B. The Pathological Changes in the Thyroid Gland as Related to the Varying Symptoms in Graves's Disease, Based on the Pathological Findings in 294 Cases, Amer. Jour. Med. Sci., 1908, cxxxvi, 851–861.

4. Wilson, Louis B. The Pathological Relationships of Exophthalmic and Simple Goitre, Surg., Gynec. and Obst., 1909, viii, 588–602; Trans. Assn. Amer. Phys., xxiii, 562–578.

5. Wilson, Louis B. The Relationship of the Clinical and Pathological Aspects of Exophthalmic Goitre, Northwest Med., 1913, pp. 1–5.

6. Wilson, Louis B. The Pathology of the Thyroid Gland in Exophthalmic Goitre, Amer. Jour. Med. Sci., 1913, cxlvi, 781–790; Trans. Assn. Amer. Phys., 1913, xxviii.

7. Wilson, Louis B. Notes on the Pathology of Simple and Exophthalmic Goitre, Med. Rec., 1913, lxxxiv, 373–378.

8. Wilson, Louis B. The Relation of the Pathology and Clinical Symptoms of Simple and Exophthalmic Goitre, Jour. Amer. Med. Assn., 1914, lxii, 111–112.

9. Wilson, Louis B. A Study of the Pathology of the Thyroids from Cases of Toxic Non-exophthalmic Goitre, Amer. Jour. Med. Sci., 1914, cxlvii, 344–351.

10. Wilson, Louis B. A Summary of the Results of Recent Investigations of the Thyroid in Relation to Symptomatic Goitre, Journal-Lancet, 1914, xxxiv, 93–97.

11. Kendall, E. C. The Determination of Iodin in Connection with Studies in Thyroid Activity, Jour. Biol. Chem., 1914, xix, 251–256.

12. Kendall, E. C. Isolation in Crystalline Form of the Compound Containing Iodin which Occurs in the Thyroid, Jour. Amer. Med. Assn., 1915, lxiv, 2042–2043.

13. Kendall, E. C. A Method for the Decomposition of the Proteins of the Thyroid with a Description of Certain Constituents, Jour. Biol. Chem., 1915, xx, 501–509.

14. Kendall, E. C. The Isolation in Crystalline Form of the Compound Containing Iodin which Occurs in the Thyroids, its Chemical Nature and Physiological Activity, Trans. Assn. Amer. Phys., 1915, xxx.

15. Smith, Ernest V., and Broders, A. C. The Iodin Content of the Thyroid Glands, with Special Reference to the Pathological Types and a Review of Some Experimental Work, Jour. Amer. Med. Assn., 1914, lxii, 113–117.

16. Plummer, H. S. Blood-pressure and Thyrotoxicosis, Trans. Assn. Amer. Phys., 1915, xxx.